PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 August 1998 (04.08.98)	
International application No. PCT/GB97/03400	**Applicant's or agent's file reference**
International filing date (day/month/year) 10 December 1997 (10.12.97)	**Priority date** (day/month/year) 10 December 1996 (10.12.96)
Applicant KING, David, John et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

08 July 1998 (08.07.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

P. Regis

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PATENT COOPERATION TREATY

REC'D 21 JAN 1999
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
P18451WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB97/03400	10/12/1997	10/12/1996
International Patent Classification (IPC) or national classification and IPC		
C07K16/00		
Applicant		
CELLTECH THERAPEUTICS LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08/07/1998	19. 01. 99
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0. Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Hinchliff , P Telephone No. (+49-89) 2399-8431

Form PCT/IPEA/409 (Cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB97/03400

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-28 as originally filed

Claims, No.:

1-10 as originally filed

Drawings, sheets:

1/14-14/14 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have b en considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The subject matter of claims 1 to 10 does not fulfill the requirements of Article 33(2) PCT because it is not novel.

1.1 British Journal of Cancer (1994), **70:1126-1130**, Pedley R. et al (D1) discloses in the materials and methods section a method of producing randomly modified Fab' which is identical to that found on p.16 of the description. It is assumed that the method disclosed in D1 allows attachment of PEG to cysteine residues on the Fab'. Consequently the subject matter of claims 1 to 10 is identical to that disclosed in D1.

1.2 WO 96 09325 (D2) discloses on p. 6, lines 20-38, a method to conjugate PEG to the thiol groups of antibodies. After PEGylation, the whole antibodies are proteolyticaly cleaved in order to produce Fab' conjugated to PEG. Consequently the subject matter of claims 1 to 10 is identical to that disclosed in D2.

Re Item VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D2 is not mentioned in the description, nor is this documents identified therein.

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 97/ 03400	10/12/1997	10/12/1996
Applicant		
CELLTECH THERAPEUTICS LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [X] None of the figures.

INTERNATIONAL SEARCH REPORT

Inte[redacted]nal Application No
PC[redacted]GB 97/03400

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K16/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PEDLEY R. B. ET AL.,: "The potential for enhanced tumour localisation by poly(ethylene glycol) modification of anti-CEA antibody" BR. J. CANCER, vol. 70, - 1994 pages 1126-1130, XP002061757 see the whole document ---	1-10
X	WO 96 09325 A (IMMUNOMEDICS INC) 28 March 1996 see the whole document ---	1-10
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
8 April 1998	24/04/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Müller, F

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHIEN-TSUN KUAN ET AL: "PSEUDOMONAS EXTOXIN A MUTANTS REPLACEMENT OF SURFACE EXPOSED RESIDUES IN DOMAIN IN WITH CYSTEINERESIDUES THAT CAN BE MODIFIED WITH POLYETHYLENE GLYCOL IN A SITE-SPECIFIC MANNER" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 269, no. 10, 11 March 1994, pages 7610-7616, XP000563744 see the whole document ---	1-10
A	WOGHIREN C. ET AL.,: "Protected Thiol-Polyethylen glycol: a new activated polymer for reversible protein modification" BIOCONJUGATE CHEM., vol. 4, - 1993 pages 314-318, XP002061758 see the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 97/03400

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9609325 A	28-03-96	US 5670132 A	23-09-97
		AU 3674995 A	09-04-96
		CA 2200482 A	28-03-96
		EP 0784634 A	23-07-97

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07K 16/00 — A1

(11) International Publication Number: WO 98/25971

(43) International Publication Date: 18 June 1998 (18.06.98)

(21) International Application Number: PCT/GB97/03400

(22) International Filing Date: 10 December 1997 (10.12.97)

(30) Priority Data:
9625640.9 10 December 1996 (10.12.96) GB

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(74) Agent: MERCER, Christopher, Paul, Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB)

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: MONOVALENT ANTIBODY FRAGMENTS

(57) Abstract

Monovalent antibody fragments are described, each of which has one or more polymer molecules site-specifically attached through a sulphur atom of a cysteine residue located outside of the variable region domain of the antibody. The polymers include synthetic or naturally occurring polymers such as polyalkylenes, polyalkenylenes, polyoxyalkylenes or polysaccharides. Each fragment may be attached to one or more effector or reporter molecules, and is of use in therapy or diagnostics where it has markedly improved binding and/or pharmacokinetic properties when compared to other antibody fragments which have the same number and type of polymer molecules, but in which the polymer molecules are randomly attached.

CLAIMS

1. A modified monovalent antibody fragment comprising a monovalent antibody fragment and at least one polymer molecule in covalent linkage characterised in that each cysteine residue located in the antibody fragment outside of the variable region domain of the fragment is either covalently linked through its sulphur atom to a polymer molecule or is in disulphide linkage with a second cysteine residue located in the fragment provided that at least one of said cysteine residues is linked to a polymer molecule.

2. An antibody fragment according to Claim 1 which is covalently linked to one, two or three polymer molecules through one, two or three cysteine residues located in the fragment outside of its variable region domain.

3. An antibody fragment according to Claim 1 or Claim 2 wherein the polymer is an optionally substituted straight or branched chain polyalkylene, polyalkenylene or polyoxyalkylene polymer or a branched or unbranched polysaccharide.

4. An antibody fragment according to Claim 3 wherein the polymer is an optionally substituted straight or branched chain poly(ethylene glycol), poly(propylene glycol) or poly(vinyl alcohol) and derivatives thereof.

5. An antibody fragment according to Claim 4 wherein the polymer is methoxy(polyethylene glycol) and derivatives thereof.

6. An antibody fragment according to any one of Claim 1 to Claim 5 in which the variable region domain is monomeric and comprises an immunoglobulin heavy (V_H) or light (V_L) chain variable domain, or is dimeric and contains V_H-V_H, V_H-V_L or V_L-V_L dimers in which the V_H and V_L chains are non-covalently associated or covalently coupled.

7. An antibody fragment according to Claim 6 wherein each V_H and/or V_L domain is covalently attached at a C-terminal amino acid to at least one other antibody domain or a fragment thereof.

8. An antibody fragment according to Claim 7 which is a Fab or Fab' fragment.

9. An antibody fragment according to any one of Claim 1 to Claim 8 covalently attached to one or more effector or reporter molecules.

10. A pharmaceutical composition comprising a monovalent antibody fragment according to any of the preceding claims together with one or more pharamaceuticaly acceptable excipients, diluents or carriers.